UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/627,787	07/27/2000	Eugen Uhlmann	02481.1679	1128

22852 7590 01/03/2002

FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Offic Action Summary	Application No. 09/627,787	Applicant(s) UHLMANN ET AL.	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,10,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information disclosure statements were received and entered as Paper Nos. 10 and 13 on 8/22/01 and 10/25/01, respectively. An amendment was received and entered as Paper No. 14 on 10/25/01. Applicant's election with traverse of the species of F3 as an aryl group; oligonucleotides as a compound to be transported; and a carboxylic acid as a reactive function, is acknowledged. Traversal is on the grounds that searching all the disclosed species would not be an undue burden. This is unpersuasive because the required searches would be non-coextensive and because the claimed conjugates are chemically distinct compounds having different structures and functions. The requirement is still deemed proper and is therefore made FINAL

Claims 1-26 remain pending in the Application. Claims 6 and 7 are withdrawn from consideration as being drawn to non-elected material. Applicant is advised that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to pharmaceutical compositions and methods of making them. The claimed composition is a conjugate of an aryl compound to an oligonucleotide. MPEP 2164.01(c) states:

> When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that use.

In this case, enablement of the claimed composition and method must be evaluated in terms of the use of the composition as a pharmaceutical. The specification fails to define the term "pharmaceutical", so in order to understand how this term limits the invention, one must determine its accepted meaning in the art. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as a "practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs." Finally, Steadman's Medical Dictionary defines "drug" as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Thus, to enable a pharmaceutical use for the claimed composition, the specification must teach how to use

the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered.

The specification teaches that the claimed compositions can be used for therapeutic and diagnostic purposes *in vivo*. Therapeutic uses of the claimed composition are discussed at page 24, line 29 to page 25, line 2 and page 25, line 27 tp page 26, line 4. The compositions are asserted to be useful for the prevention and treatment of diseases caused by overexpression of certain genes, particularly viral diseases, cancer, restenosis, and depigmentation diseases. See page 25, line 30 to page 26, line 4. Treatment can be effected by delivery of antisense oligonucleotides; triplex-forming oligonucleotides; "decoy" oligonucleotides which mimic the binding site of transcription factors, titrating these factors and inhibiting binding to their natural targets; and chimeraplasts for site-directed gene modification. Thus the claims broadly embrace the treatment or prevention of any disease caused by gene overexpression.

The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch

(Trends in Biochem Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) teach that although antisense therapy is simple in theory, it " has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors conclude that [c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) teaches that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value.

Gryzanov (Biochim. Biophys. Acta 1489:131-140, 1999) set forth the state of the art with respect to therapeutic applications of triple helix technology. Gryzanov notes that "several

important issues remain to be resolved before oligonucleotides may become widely used unique and specific pharmaceutical agents. Among these are: increased thermodynamic stability of the complexes formed by the oligomers with their nucleic acid targets, specificity of the interactions, resistance to enzymatic degradation and hydrolytic stability in cells, in model animal systems, and importantly, favorable pharmacokinetics and biodistribution in human tissues and organs. Additionally, chemical structures of the therapeutic oligonucleotides, cost of synthesis, and the proper choice of suitable and biologically important molecular targets, as well as delivery methods for administration of compounds, will play a crucial role in ensuring success of oligonucleotide-based therapeutic approaches." See page 132, lines 31-37 of column 1 to line 10 of column 2.

The instant invention addresses the aspect of oligonucleotide (ODN) delivery. The specification indicates that the invention serves to (a) improve delivery by increasing the rate at which ODNs are taken up by cells, (b) circumvent the endocytotic pathway thereby allowing distribution of ODNs to both the cytosol and nucleus, and (c) decrease the damage to cells compared to liposomal delivery compositions. See page 4, line 28 to page 5, line 19. A variety of oligonucleotides designed for the treatment of various diseases is disclosed at pages 13-17. The specification teaches working examples demonstrating the uptake of the claimed compositions into cultured cells *in vitro*. See Tables 1 and 2 on pages 37 and 38, and also Fig. 9.

The specification does not disclose the effect of the compositions on any cell, or provide any working example of any therapeutic effect. No specific therapeutic or preventative protocol

for any disease is taught. No specific guidance is given with respect to dosages or routes of delivery for any particular disease. No evidence is provided that the increased rate of uptake, and improved cellular distribution observed in the instant invention are sufficient to overcome the art-recognized problems associated with therapeutic oligonucleotide delivery as set forth by Crook. The specification fails to account for various critical factors which will influence the success of therapy including the varying concentrations and stabilities of the target mRNAs or polypeptides, the thermodynamic stability of complexes formed by the compositions, the specificity of the interactions, stability of the preparations in animal systems, and pharmacokinetics and biodistribution in human tissues and organs. Perhaps most importantly, none of these issues has been considered within the context of any one therapeutic protocol. Because the physiological art is recognized as being unpredictable (MPEP 2164.03), one of skill in the art recognizes that these variables will change with the identity of the disease to be treated or prevented. However, the specification fails to address the variables cited above in the context of treating or preventing any specific disease. Furthermore, given the unpredictability of oligonucleotide design, as set forth by Branch, it is unclear that any of the oligos taught in the specification will have any therapeutic effect *in vivo*.

Given the unpredictable state of the art of oligonucleotide-mediated therapies, the lack of guidance and working examples in the specification, and the breadth of diseases disclosed as treatable with the claimed compositions, one of skill in the art could not use the claimed invention as intended without undue experimentation.

The specification also teaches that the claimed compositions can be used for *in vivo* diagnosis of diseases caused by the overexpression of genes. See page 24, line 29 to page 25, line 2. However, no guidance is given as to how the claimed compositions may used *in vivo* as a diagnostic. A search of the prior art revealed only two publications related to the *in vivo* use of oligonucleotides for diagnosis, both from the same laboratory. Rusckowski et al (Cancer 80(12)(Supplement): 2699-2705, 1997) and Mardirossian (J Nucl. Med 38(6): 907-913, 1997) teach the use of oligonucleotides in pretargeting techniques. Briefly, a target entity such as a bacterium or a tumor cell was injected in to the left thigh of a mouse, Then an oligonucleotide, conjugated to a molecule with an affinity for the target entity, was injected into the mouse. Subsequently a complementary, radioactively-labeled oligonucleotide was injected and allowed to hybridize to the first oligonucleotide. Although the resulting signal was detected in the target tissue, it was also associated with liver, heart, kidneys, lung, stomach, spleen, intestines and blood, in amounts greater than in the target tissue. See Rusckowski, Table 1 on page 2702, and Figs. 2 and 3 on pages 2703 and 2704. Clearly the level of false positive signal in these tissues shows that the technique did not have diagnostic value at the time of publication. The instant specification fails to contemplate this specific use for the claimed invention, and thus does not provide any teachings which would improve the technique to the point that it could function as an *in vivo* diagnostic.

Because the specification provides no guidance as to how to use the claimed invention in vivo as a diagnostic tool, and because the state of the art shows that oligonucleotide compositions

were not routinely used for this purpose by those of skill in the art, one of skill in the art would have to perform undue experimentation to use the claimed compositions *in vivo* as diagnostics.

This rejection can be overcome by deleting the word pharmaceutical from the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5-7, 9, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite because it recites the term "modified", which is a relative term. The term "modified" is not defined by the claim, the specification does not provide a standard for determining what constitutes a modified oligonucleotide. One of skill in the art is left to ask, “Modified relative to what?”. Thus the metes and bounds of the claim are unclear.

Claims 6 and 7 are indefinite because they recite the term "low", which is a relative term. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, the parameter of “molecular weight” is rendered indefinite by the use of the term “low”. It is noted that claim 6 stipulates that the compound must have a molecular weight below 500 D. However, it is not clear form the claims

or the specification that all compounds of less than 500 D are considered to be "low" molecular weight compounds. In other words, "low" could conceivably refer to compounds of less than 300 D. In this case, compounds greater than 300 D and less than 500 D would not be considered to be "low" molecular weight.

Claim 9 is indefinite because it recites chemical structures employing non-standard nomenclature. Structures F1-F11 each contain what appears to be a carbonyl or sulfonyl group to which is attached a squiggly line. The specification does not disclose what the squiggly line represents, and it does not appear to be standard nomenclature in the art, so the claim is confusing.

Claim 16 is indefinite because the method steps are not concordant with the purpose set forth in the preamble. Although the preamble requires transport across a membrane, the method recites no active step in which transport occurs.

Conclusion

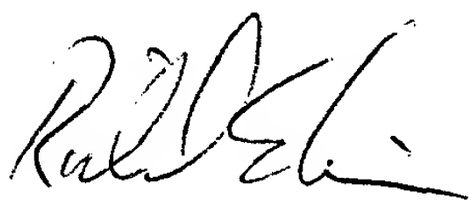
No claim is allowed. The elected species of a conjugate comprising F3 as an aryl group; oligonucleotides as a compound to be transported; and a carboxylic acid as a reactive function is allowable, however claims 1-5 and 8-26 are objected to as being drawn to non-elected material. These claims embrace species other than those elected.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch, can be reached at 703-308-1126. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.



Richard Schnizer, Ph.D.